UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,256	12/09/2003	John Gavin MacDonald	KCX-859 (19100)	4720

22827 7590 05/12/2009

DORITY & MANNING, P.A.
POST OFFICE BOX 1449
GREENVILLE, SC 29602-1449

EXAMINER	
SCHLIENTZ, NATHAN W	
ART UNIT	PAPER NUMBER
1616	
MAIL DATE	DELIVERY MODE
05/12/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/731,256
Filing Date: December 09, 2003
Appellant(s): MACDONALD ET AL.

Ryan P. Harris
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 23 February 2009 appealing from the Office action mailed 05 September 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner. The rejection of claims 62 and 63 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is hereby withdrawn by the examiner.

Also, the examiner duplicated the rejection of claims 28, 30, 31, 33-35, 37, 38, 40, 42-44, 46, 64 and 65 under 35 U.S.C. 103(a) as being unpatentable over Bosch et

al. in view of Breitbarth and Ma et al. Therefore, the rejection is stated only once in the present Examiner's Answer.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,597,575	BREITBARTH	01-1997
6,548,264	TAN ET AL.	05-2000
WO 03/032959	BOSCH ET AL.	04-2003

Ma et al., "Adsorption of Proteins and Antibiotics on Porous Alumina Membranes" Fundamentals of Adsorption, Vol 80 (1992), pp. 389-396.

Marta E. Daraio and Enrique San Roman, "Aggregation and Photophysics of Rose Bengal in Alumina-Coated Colloidal Suspensions", Helvetica Chimica Acta, 2001, Vol. 84, 2601-2614.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 28, 30, 31, 33-35, 37, 38, 40, 42-44, 46, 64 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosch et al. (WO 03/032959) in view of Breitbarth (US 5,597,575) and Ma et al. (Fundamentals of Adsorption, 1992), as evidenced by Daraio et al. (Helvetica Chimica Acta, 2001).

Appellant's claims

Appellants claim a method of utilizing a triggerably releasable delivery system comprising administering to the mucosal membrane alumina coated silica nanoparticles with a functional compound bound to the surface, wherein a change in pH releases the functional compound.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Bosch et al. teach compositions comprising at least one type of inorganic core having absorbed or bound to the surface thereof at least one type of active molecule (Abstract; pg. 1, ll. 3-4; pg. 5, ll. 15-27; and pg. 9, ll. 4-7). Bosch et al. teach that the inorganic core may have a particle size wherein 50%, 60%, 70%, 80% or 90% of the particles are less than about 1 μm, less than about 800 nm, less than about 700 nm,

less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, less than about 500 nm, less than about 25 nm, less than about 15 nm, less than about 10 nm, or less than about 50 nm (pg. 10, ll. 15-26), wherein exemplary cores, suitable for pharmaceutical and other uses, are nanoparticulate silica, alumina, and hematite (pg. 10, ll. 1-2). Bosch et al. also teach that the active agent may be useful in mucosal applications, wherein exemplary active agents include dental applications, such as oral nanoparticulate lidocain formulations and nanoparticulate fluoride treatments, application to the lungs, throat, gastrointestinal (GI) tract, application to wounds, etc. (pg. 14, ll. 12-20). Bosch et al. teach that pharmaceutical therapeutic methodologies for mucosal applications include colonic, oral, rectal, intravaginal, injectable (e.g., intravenous or subcutaneous), pulmonary, nasal, buccal, topical, local, intracisternal, intraperitoneal, ocular, aural, transdermal, buccal spray, or nasal spray administration (pg. 14, ll. 21-24; and pg. 22, ll. 11-15). Bosch et al. also teach that pharmaceutical compositions according to their invention may also comprise one or more binding agents, filling agents, lubricating agents, suspending agents, sweeteners, flavoring agents, preservatives (i.e., methylparaben, propylparaben, butylparaben, ethyl alcohol, benzyl alcohol, and benzalkonium chloride), buffers, wetting agents, disintegrants, effervescent agents, and other excipients (pg. 20, ll. 8-11). Bosch et al. also teach that the composition can be in the form of a solution, suspension, syrup or elixir or as formulated for solid dose administration (pg. 24, ll. 3-5).

Bosch et al. further teach specific examples wherein Nalco alumina particles with a particle size of 8 nm have naproxen or ketoprofen bound to the surface, as determined by attenuated total reflection infrared spectroscopy (ATR-FTIR), electrokinetic measurements and thermogravimetric analysis (TGA) (Examples 1-3). Nalco 1056 are positively charged alumina coated silica nanoparticles, as evidenced by Daraio et al. (pg. 2603, Experimental).

Bosch et al. also show that the zeta potential of alumina, silica, and alumina coated silica particles are a function of pH and drug concentration and are capable of being above 40 mV (Figures 1, 2, 11, 12 and 18).

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Bosch et al. do not teach the active molecule is released from the nanoparticle upon administration to a mucosal membrane as a result of a change in the pH. However, Breitbarth teaches that topical application for administering drugs and even controlled release of drugs is now used extensively (col. 3, ll. 32-34). Breitbarth teaches that it is readily known to adsorb active agents to silica, alumina, or coated silica particles, wherein the active agent can readily and controllably be released from the particles by a small pH change (col. 5, ll. 11-18). Also, Ma et al. clearly teach that the adsorption of tetracycline on the surface of alumina membranes is pH dependent, wherein a change in pH of either acidic or basic change results in the release of tetracycline (Abstract; Introduction 2nd paragraph; Results and Discussion 1st paragraph; Figures 1 and 2; and Table 1).

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one skilled in the art at the time of the invention to apply the alumina coated silica nanoparticles with active agents adsorbed thereon to mucosal membranes, as taught by Bosch et al., with the expectation that a small change in pH will readily and controllably release the active agent from the surface of the nanoparticles, as reasonably taught by Breitbarth and Ma et al.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

2. Claims 28, 30, 31, 33-35, 37, 38, 40, 42-44, 46, 64 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tan et al. (US 6,548,264) in view of Bosch et al. (WO 03/032959), Breitbarth (US 5,597,575) and Ma et al. (Fundamentals of Adsorption, 1992), as evidenced by Daraio et al. (Helvetica Chimica Acta, 2001).

Appellant's claims

Appellants claim a method comprising administering to a patient a plurality of nanoparticles containing silica coated with alumina that are about 500 nm or less, wherein the alumina provides a site on a surface to which is bonded a functional

compound that is released in response to exposure to an environmental or chemical condition, and the nanoparticles possess a zeta potential of about 20 mV or more.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Tan et al. teach silica-coated nanoparticles, wherein the nanoparticles comprise a core coated with a shell, such as mixtures or layers of silica and alumina, and derivatized with functional groups on the surface thereof, which can be used as drug molecule particles (Figure 1; column 2, lines 9-14 and 24-25; column 5, lines 55-60 and 67; column 6, lines 1-4 and 36-44; and column 11, line 62 through column 12, line 1). Tan et al. further teach that the nanoparticles are preferably between about 10 nm to about 300 nm (column 4, lines 26-35), and can be dispersed in a pharmaceutically acceptable carrier and administered to a patient (column 12, lines 1-4). Also, Tan et al. teach that drugs coated onto the nanoparticles can be further contained within a time-release coating (i.e. biodegradable sugar) so that the drug can accumulate at the site before becoming active (column 12, lines 7-10).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Tan et al. do not explicitly teach nanoparticles containing silica coated with alumina wherein the nanoparticles are administered to a mucosal membrane of a patient. However, Tan et al. do teach that the nanoparticles comprise a shell that can be composed of an inorganic oxide such as alumina or silica, or mixtures of the foregoing, and the shell can include a first layer of silica coating and immediately

adjacent to the core, and a second layer coating the silica layer (column 5, lines 55-60 and 67; and column 6, lines 1-4). Also, Bosch et al. teach compositions comprising at least one type of inorganic core having absorbed or bound to the surface thereof at least one type of active molecule (Abstract; pg. 1, ll. 3-4; pg. 5, ll. 15-27; and pg. 9, ll. 4-7), wherein exemplary cores, suitable for pharmaceutical and other uses, are nanoparticulate silica, alumina, and hematite (pg. 10, ll. 1-2). Bosch et al. also teach that the active agent may be useful in mucosal applications (pg. 14, ll. 12-20) and that pharmaceutical therapeutic methodologies for mucosal applications include colonic, oral, rectal, intravaginal, injectable (e.g., intravenous or subcutaneous), pulmonary, nasal, buccal, topical, local, intracisternal, intraperitoneal, ocular, aural, transdermal, buccal spray, or nasal spray administration (pg. 14, ll. 21-24; and pg. 22, ll. 11-15). Specific nanoparticles taught by Bosch et al. include Ludox CL and Nalco alumina particles (Examples 1-3).

Tan et al. also do not teach the functional compounds are released from the nanoparticles as a result in a change in pH. However, Breitbarth teaches that topical application for administering drugs and even controlled release of drugs is now used extensively (col. 3, ll. 32-34). Breitbarth teaches that it is readily known to adsorb active agents to silica, alumina, or coated silica particles, wherein the active agent can readily and controllably be released from the particles by a small pH change (col. 5, ll. 11-18). Also, Ma et al. clearly teach that the adsorption of tetracycline on the surface of alumina membranes is pH dependent, wherein a change in pH of either acidic or basic change

results in the release of the tetracycline (Abstract; Introduction 2nd paragraph; Results and Discussion 1st paragraph; Figures 1 and 2; and Table 1).

With regard to the zeta potential of the nanoparticles of Tan et al., Bosch et al. clearly show that the zeta potential of alumina, silica, and alumina coated silica particles are a function of pH and drug concentration and are capable of being above 40 mV (Figures 1, 2, 11, 12 and 18).

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one skilled in the art at the time of the invention to make the nanoparticles of Tan et al. comprising a core coated with a shell that is functionalized with a chemical or biological group and administering the nanoparticles to a patient, wherein the shell comprises silica coated with alumina, as reasonably taught by Tan et al.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(10) Response to Argument

Appellant's Remarks filed in the Appeal Brief have been fully considered but they are not found persuasive.

Appellants argue on page 7 of the Appeal Brief that the examiner failed to address the limitation that the nanoparticles are contained within a vehicle that further comprises a pH altering material. The examiner respectfully argues that the compositions of Bosch et al. are formulated for oral, rectal, intravaginal, buccal, nasal, etc. administration (pg. 22, ln. 10 through pg. 23, ln. 23), wherein the formulations are solid or liquid and comprise carriers, diluents, solvents, vehicles, inert excipients, fillers, extenders, binders, humectants, wetting agents, adsorbents, lubricants, and *buffers*. Therefore, the compositions comprise a vehicle (the dosage form being either a solid or liquid) and a pH altering material, such as a buffer.

Appellants argue on page 9 that in contrast to Bosch et al. and Appellant's invention, Breitbarth teaches particle sizes that are bigger than instantly claimed, that the microparticles have a negative surface charge, and they are not directed to application to mucosal membranes. However, the examiner respectfully argues that Breitbarth was relied upon for the general knowledge in the art that active agents bound to the surface of particles can be released by a change in pH (col. 5, ln. 10-20).

Appellants further argue on page 10 that the examiner has failed to point to any disclosure that would obviate applying nanoparticles with a zeta potential of +20 mV or more and a functional compound bonded thereto to a mucosal membrane wherein the functional compound is released from the surface of the nanoparticles upon exposure to a change in pH. However, the examiner respectfully argues that Bosch et al. teach binding active agents to the surface of silica and/or alumina nanoparticles, wherein the nanoparticles have a zeta potential of +20 mV or more (Abstract; pg. 5, ln. 15-19;

Figures 1, 2, 11, 12, 18 and 19). Bosch et al. specifically teach alumina coated silica nanoparticles called Ludox CL (Examples 2 and 6), which are also disclosed in the instant specification on pg. 9, ln. 3-5 as examples of alumina coated silica nanoparticles that meet the limitations of the instant invention. Bosch et al. further teach that the zeta potential of the nanoparticles is pH dependent, wherein from acidic to neutral pH the nanoparticles have a zeta potential of +20 mV or more (Figures 1 and 11). Also, Bosch et al. teach administering the formulations to the mucosal membranes, such as the GI tract, lungs, throat, vagina, nasal passage, the oral mucosa, etc., as discussed above, which have differences in pH. Therefore, upon administration of the formulations of Bosch et al., the compositions experience a change in pH.

Thus, Bosch et al. teach binding an active agent to the surface of a nanoparticle with a zeta potential above +20 mV, wherein upon administration of the composition to the mucosa where a change in pH will occur, the active agent is administered to the patient.

Appellants also argue on page 10 that Ma et al. do not teach that after adsorption onto the alumina membranes, a change in pH forces the release of the compound from the surface. However, the examiner respectfully argues that Ma et al. teach tetracycline adsorption onto alumina membranes is greatest at pH near 5, wherein at pH of 2.6, 7 and 8.3 the tetracycline adsorption onto alumina membranes was lower. As stated by Appellants, Ma indicates that the amount adsorbed onto the surface of alumina membranes is pH dependent. Therefore, one of ordinary skill in the art would

reasonably understand that at pH above and below 5 the amount of tetracycline that adsorbs to alumina is less than at pH 5.

Therefore, in view of the combined teachings of Bosch et al., Breitbarth and Ma et al., one of ordinary skill in the art would have a reasonable expectation of success in preparing alumina coated silica nanoparticles with an active agent bound to the surface thereof for mucosal administration, as taught by Bosch et al., wherein the active agent is tetracycline and is bound the alumina surface and is released upon a change in pH, such as when administered to the mucosa.

Appellants argue on page 12 that Tan et al. do not reasonably teach silica coated with alumina. However, as mentioned by Appellants, Tan et al. teach core shell nanoparticles wherein the shell can be silica or alumina. Also, Bosch et al. clearly teach silica coated with alumina nanoparticles. Therefore, one of ordinary skill in the art would reasonably known how to use alumina coated silica for adhering an active agent to the surface thereof.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Johann R. Richter/

Supervisory Patent Examiner, Art Unit 1616

Conferees:

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617

/Nathan W Schlientz/

Examiner, Art Unit 1616